11-8-90

008574

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

219 AA

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No./File Symbol 464-AUC
XRM 5184 TC Termiticide Concentrate

FROM: Lucy P. Markarian 10/31/90
Precautionary Review Section
Registration Support Branch
Registration Division (H75-05C)

11/8/90

TO: Dennis Edwards/Carl Andreasen (PM 12)
Insecticide - Rodenticide
Registration Division (H75-05C)

APPLICANT: Dow Elanco
9002 Purdue Road
P.O Box 68128
Indianapolis, IN 46268-1189

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt.
Chlorpyrifos [O,O-diethyl O-(3,5,6-Trichloro-2-pyridinyl) phosphorothioate	22.0%
Inert Ingredient(s):	78.0%
Total	100.0%

BACKGROUND:

Dow Elanco has presented five acute studies in support of their product XRM-5184 TC under EPA Symbol 464-AUO. XRM-5184 has 22.0% chlorpyrifos as active ingredient and 78.0% inert's [redacted]. Formerly an oral LD50 study was submitted and accepted as core minimum data. The present package includes the five remaining required acute toxicity studies.

RECOMMENDATION:

A. The eye and Dermal irritation studies are accepted as core guideline data

B. The sensitization study is considered core minimum data, but accepted. The reasons for the grading are:

1. The guidelines require that the method must be specified when conducting the test. This was not done, it was assumed that the Buehler method was used.
2. The Buehler method includes naive controls as a base for comparison. There were no naive controls included in the test. The positive controls serve to demonstrate the capability of the performing laboratory to induce sensitization and are not used as points of comparison.
3. Only male animals were used. The guidelines require representation of both sexes.

RECOMMENDATION: cat. 008574

C. The Acute Dermal Toxicity test is considered supplemental data for the following reasons:

1. The animals are overweight. The guidelines specify that the animals used in testing dermal toxicity must be in the 2.0 to 3.0 kg range. The weight is indicative of age. An overweight animal is often older than the required young adult rabbit. Furthermore, it is established in the principles of toxicology that age and weight are definite variants in toxic responses, and the results obtained from overweight and old animals are not reliable.

2. Animals must not be washed with soap, regardless of how mild it is, to remove residue. Soap adds a variable to the test condition.

D. The inhalation study is considered supplemental data for the following reasons:

1. Some of the animals are immature and underweight. A 105 gm Fischer rat is not considered a young adult. As discussed before, age and weight have a definite bearing on the toxic responses. An immature and/or underweight animal responds differently to a test material than an young adult, and as result the outcome of the test is not reliable. The females in the test weighed more less than the males and there was a higher incidence of mortality in the females. It cannot be decided if the higher rate of mortality was due to the immaturity

RECOMMENDATION: (Cont)

of the females or There was in effect a sex difference in the toxicity of XRM 5184. The oral toxicity did not indicate a sex difference.

2. There was more than 20% difference in weights of the animals among the different levels. The guidelines state that "The weight variation of animals or between groups of animals used in the Test should not exceed 20% of the mean weight of each sex." The males at 1.90 mg/L were considerably heavier than the females in the 5.09 mg/L group and 1.90 mg/L group (200g versus 112 & 134g)

3. All dose levels must include male and female. The lowest level is conducted using females only. The recommendation for using fewest possible animals does not mean to sustain the use of animals to such a degree as to render the test results unreliable. The objective remains to be safety. The guidelines require that if the limit Test indicates a three level LC_{50} study five of each sex must be used per level.

4. Statistical analysis is required by the guidelines when a three level LC_{50} study is conducted. Statistical analysis is not feasible with just five animals at one level

5. The sampling rates for the gravimetric analyses or particle sizing must be included.

6. MMAD is expressed as an average for the whole test (for all levels). This is not acceptable. Information specific

RECOMMENDATION: (cont)

To particle size determination for each level must be provided. The information must include the particle sizes at each stage of the impater, their distribution in weight and percentage, specific MMAD for that analysis and the standard geometric deviation.

It is recommended That Dow Elanco present new data in:

1. Dermal Toxicity - using the right animal weight ranges and not introducing variables that are

2. Inhalation Toxicity - using animals in the right weight and weight range, in equal male/female numbers

b. Include information about particle size and distribution as explained

c. Provide statistical analysis - 95% confidence limits as required by the guidelines.

Label

As The tests stand now the signal word is 'caution'

The precautionary statement must include:

Harmful if swallowed or absorbed Through skin or Inhaled

delete "causes moderate eye irritation"

"handle concentrate in a ventilated area"

"wear protective clothing + Chemically resistant gloves when handling"

The statement of practical treatment is adequate as it is

The label may have to be revised after the receipt + review of the requested data.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (§81-2)

Product Manager: (12) Reviewer: L. Markarian
MRID No.: 416401-01 Report Date: 10/31/90
Testing Laboratory: Tox. Research Dow Chemical Report No. M-005184-001
Author(s): N.M. Bardsley, D.J. Schuetz, B.L. Yano
Species: Rabbit, New-Zealand white (Hazleton Research Products, Inc. Kalamazoo MI
Sex : 5♂ & 5♀ Wt.: 3.1 - 3.6kg
Test Material: Chlorpyrifos (GHD-2653-3) AFR221870) (XRM 5134) examined
Quality Assurance (40 CFR §160.12): included

Summary:

1. LD_{50} (mg/kg): Males = _____; Females = _____; Combined = _____;
2. The estimated LD_{50} is _____.
3. Tox. Category: _____. Classification: Supplementary

Procedure (Deviations From §81-2): The test material was applied to the shaved backs of rabbits, held in contact with gauze dressing & tape & plastic wrap (non-occlusive) for 24hr. The trunks. At 24hr wrappings were removed, The skin was wiped with soap and water & dried with disposable towels & collars were placed around the necks to avoid ingestion for 24hr. Observations were frequent in the day of dosing and daily thereafter, weights were recorded at intervals on days 2, 8, & 15. Necropsy was performed on all rabbits, CO_2 euthanized

Results:

Reported Mortality

DOSAGE (mg/kg)	(NUMBER KILLED/NUMBER TESTED)		
	Males	Females	Combined
2000	0/5	0/5	0/10

Symptomology & Gross Necropsy Findings:

There were no deaths. No systemic toxicity was observed. Dermal toxicity was expressed as erythema (10/10) with three males showing exfoliation at the application site. Duration of erythema not specified. No treatment related gross pathology was observed at Terminal necropsy.

6

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (§81-3)

Product Manager: (12) Reviewer: L. Markarian
MRID No.: 416401-02 Report Date: 10/3/90
Testing Laboratory: Tox. Research, Dow Chemical Report No. M-005184-003
Author(s): G.J. Bradley, J.E Battles, K.E. Stebbins
Species: Rat, Fischer 344
Sex : 10 ♂ 15 ♀ Weight: 106.5 - 206.1 g
Source: Charles River Breeding Laboratories, Inc. Kingston, N.Y.
Test Material: Chlorpyrifos (GHD-2635, Lot #22,270) (XRM5184) clear liquid
Quality Assurance (40 CFR §160.12): Included

Summary:

1. LC_{50} (mg/kg): Males = _____; Females = _____; Combined = _____
2. The estimated LC_{50} is _____
3. Mean Concentration: _____
4. Tox. Category : _____. Classification: Supplementary

Procedure (Deviations From §81-2): 42L (30cm inside diameter x 60cm h) chamber was used for nose only exposure of rats. System was airtight & to maintain temperature at 22° and humidity at 50%. Airflow was maintained at 3.2 L/min. Aerosol was generated by metering the test material with FMI pump (Fluid metering Inc. Oyster Bay, NY) into a stainless steel ¼ J spray nozzle (Spraying Systems) The aerosol was mixed with compressed air in the spray nozzle & into the chamber. 30L/min of oxygenated air used for aerosol generation. Air flow was determined using a calibrated flowmeter. Air flow, Temperature & humidity were recorded at 30 minute intervals. Gravimetric determination of chamber concentrations

Results:

Reported Mortality

Exposure Concentration (mg/L)	(NUMBER KILLED/NUMBER TESTED) Males	Females	Combined
5.09 (4.78-5.37)	5/5	5/5	10/10
1.90 (1.67-1.98)	1/5	4/5	5/10
1.14 (0.95-1.25)	—	0/5	0/5

were made three times during the exposure from the breathing zone. Sampling rate not specified. Particle size determinations were made twice per exposure and from the breathing zone using a six stage Sierra Instruments Cascade impactor at unspecified sampling rate. MMAD was expressed as 1.90 um with the standard deviation at 2.13 as an average for all three levels. No individual MMAD or particle size distribution presented.

Animals were observed during exposure and once daily thereafter. Body weights were recorded at initiation and on days 2, 4, 8, 11 & 15, except females at 1.14 mg/L. The weights were not recorded on day 2.

Necropsy was performed on all animals at death or at termination.

Results

At 5.09 mg/L all died within 2 days. Signs of toxicity included soiled fur, [illegible], breathing through mouth, regurgitating action, slow movement & lethargy. Necropsy revealed gaseous [illegible] as gas and/or homolyzed blood in the GI tract and [illegible] recessment [illegible] on the glandular [illegible] of the stomach. Additionally soiling of the perineal area [illegible] was noted. Corpus [illegible] and distended [illegible] was observed, but attributed to spontaneous occurrence. Other observations as congested viscera, decreased fat [illegible] were attributed to "agonal or stress related changes"

Similar signs of toxicity were observed at 1.90 mg/L. The one male died on Till day 13. One female had a discolored foot interpreted as "cyanosis of distal extremities." Gross pathology was also similar to the higher dose level except that the surviving female showed no abnormalities.

Weight loss was recorded at this level on day 2 (12%) and the animals continued to lose weight to termination.

At 1.14 mg/L soiling of fur, breathing through mouth, redness at nares & regurgitating action were noted. However all were normal by day 6. 9% loss in body weight was noted on day 4, but the animals had gained weight at termination.

Necropsy revealed no abnormalities

DATA REVIEW FOR ACUTE EYE IRRITATION TESTING (§81-4)

Product Manager: (12)
MRID No.: 416401-03
Testing Laboratory: Tox. Research, Dow Chemical
Author(s): N.M. Bardasco
Species: Rabbit, New Zealand White
Sex: 3♂ + 3♀ Weight: 2.9 - 3.4 kg
Source: Harleton Research Products, Inc. Denver Pa
Dosage: 0.1 ml
Test Material: Chlorpyrifos (GHD-2653-3, AGE 28.1790) XRM 5124 (clear liquid)
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markarian
Report Date: 10/31/90
Report No. M-005124-005-C

Summary:

Tox. Category: IV Classification: Core Guideline

Procedure (Deviation From §81-4): The test material was instilled in the conjunctival sac of pre-examined right eyes. All were observed immediately with penlight at 1, 24, 48 + 72 hrs after instillation. Grading was done according to Draize.

Results:

Observations (number "positive"/number tested)

	Hour	Days					
	1	1	2	3	4	7	14	21
Cornea Opacity	0/6	0/6	0/6	0/6				
Iris	0/6	0/6	0/6	0/6				
Conjunctivae Redness	6/6	5/6	3/6	0/6				
Chemosis	0/6	0/6	0/6	0/6				
Discharge	4/6	0/6	0/6	0/6				

Comments: Animals over 3.0 kg must not be used. They are not considered young adults at that weight.

DATA REVIEW FOR SKIN IRRITATION TESTING (§81-5)

Product Manager: (12)
MRID No.: 416401-04
Testing Laboratory: Tox. Research, Dow Chemical
Author(s): N.M. Bercaso
Species: Rabbit, New Zealand white Hazleton Research Products, Inc. Denver, P
Age: not specified
Sex: 3♂ + 3♀
Weight: 2.7 - 3.1 kg
Dosage: 0.5 ml
Test Material: Chlorpyrifos GH-2522-47 XRM 5184 unlabeled
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markarian
Report Date: 10/31/90
Report No. M-005184-002-13

Summary:

The Primary Irritation Index = 0

Toxicity Category: IV

Classification: Core guideline

Procedure (Deviations From §81-5): Test material was applied to the shaved backs of rabbits under 4"x4" gauze patch & type. This was covered with flannel bandage & taped to the rabbit. After the wrappings were removed the remaining residue was removed with damp tissue. Sites were graded according to Draize at 30min, 24, 48, 72 hrs after removal of patches.

Results:

No irritation was observed at any of the sites at any interval

Special Comments:

iv

005574

DATA REVIEW FOR SKIN SENSITIZATION TESTING (§81-6)

Product Manager: (12)
MRID No.: 416401-05
Testing Laboratory: Tox. Research, Dow Chemical
Author(s): N.M. Berdasco
Species: Guinea Pig, Hartley
Sex: Male Weight: 400-456
Source: Charles River Breeding Laboratories, Inc. Kingston NY
Test Material: Chlorpyrifos GHD 2635-3 (XRM-5184) Clear liquid
Positive Control Material: 10% DER 331 epoxy resin in dipropylene glycol monomethyl ether
Quality Assurance (40 CFR §160.12): included

Reviewer: Lucy D. Markarian
Report Date: 10/31/90
Report No. M 005184-001
M 005282-001

Method: not specified, assumed to be Buehler

Summary:
1. This product ~~is~~ (is not a dermal sensitizer
2. Classification: core minimum

Procedure (Deviation From §81-6): A pretest screening was made using 2 guinea pigs and Two concentrations: 100% & 50% N.E. irritation was observed at any site Therefore undiluted (100%) test material was used for induction and elicitation.
Two Groups of 10 guinea pigs were used. One group was induced with 100% Test material and the other with 10% DER. The DER was diluted to 7.5% after irritation was observed at the second application. Three

Three applications of 0.4ml in Hill Top chambers in each group. The chambers were secured with Tape. Each application was for 6 hrs. Observations were made (system unspecified) 24 hrs after each induction. 2 weeks after the last induction challenge was made using 10% Test material in the Test group and 5% DER in the positive control group applied as the induction applications. At 6 hrs the chambers were removed and the irritation scored at 24 & 48 hrs.

There were no naive controls.

Results

No irritation was noted after any of the induction applications or at 24 or 48 hrs after challenge with the Test material.

DER 331 resulted in mild irritation at 5/10 sites after the 3rd induction. At challenge at 24 hrs 3/10 were positive and at 48 hrs 7/10 were positive.